REMARKS

Claims 1-3, 5-8, 10, 11, 13, 14, 16-20 and 26 presently appear in this case. No claims have been allowed. Claims 17-20 have been withdrawn from consideration. The Official Action of March 26, 2010, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a lipid assembly which includes a biologically active non-liposome forming lipid, a lipopolymer, and a liposome forming lipid. The biologically active non-liposome forming lipid has a hydrophobic region and a polymer headgroup wherein the atomic mass ratio between the head group and the hydrophobic region is less than 0.3. The lipopolymer has a hydrophobic lipid region and a hydrophilic polymer headgroup and a atomic mass ratio between the head group and the hydrophobic region is at least 1.5. The components of the lipid assembly are selected such that the lipid assembly is chemically and physically stable under storage conditions of 4°C in biological fluids for at least six months. The invention also relates to a pharmaceutical composition comprising the lipid assembly and a physiologically acceptable carrier. The lipid assembly is present in an

amount sufficient to achieve a biological effect at a target site.

The interview, conducted on September 22, 2010, among Examiners Isaac Shomer, Jeffrey Lundgren and Brian Gulledge and the undersigned attorney is hereby gratefully acknowledged. In this interview, the undersigned attorney pointed to places in the present specification that indicated that those of ordinary skill in the art would not expect that the preferred compositions of the Wei reference would have long term stability. It was further explained why adding a lipopolymer such as polyethylene glycol (PEG) would not be expected to create such stability. The examiners were shown a proposed amendment to claim 1 that would further clarify that the components must be selected such that the long term stability is obtained. The amendment discussed at the interview is the same as that presented herewith and the arguments presented in the interview will be repeated in detail hereinbelow. As a result of the interview, the examiners suggested that the arguments about unexpected results be placed in the form of a declaration and submitted in order to make the record more clear and that analytical data as to the stability column of Table 4 of the present specification should be provided in such a declaration. The examiners also stated that

applicant should ensure that the claims are commensurate in scope with the evidence of unexpected results relating to stability.

Claim 14 has been objected to for using the term "comprises a phospholipid." The examiner suggests amending the claim to read "is a phospholipid".

Claim 14 has now been amended to accept the suggestion of the examiner, thus obviating this objection.

Claims 1, 2, 4, 5, 10, 14, 16 and 26 have been rejected under 35 USC 103(a) as being unpatentable over Wei as evidenced by Kumar. The examiner has previously stated that Wei, in Example 7, discloses liposomal formulations of C2 and C6 ceramides and that Tables 5 and 6 further show that liposomes were prepared with free non-silylated C6 ceramides as well as silylated C6 ceramides. The examiner states that the liposome of Wei includes phosphatidylcholine (PC). The examiner has conceded that Wei does not anticipate as it teaches no example falling within the scope of the present claims, but the examiner considers it to be have been obvious to have engaged in picking and choosing from among the various combinations of disclosed ingredients so as to include a lipopolymer along with the PC and ceramide. The examiner considers that such a composition would yield no more than one would expect from such an

arrangement. The examiner has conceded that Wei does not teach that the lipid assembly is stable at 4°C for six months but states that this would be an expected property of a lipid assembly consisting of ceramide and pegylated lipid as there are no oxidatively labile groups in ceramide and it is shielded due to the presence of PEG. In the latest rejection, the examiner states, with respect to the issue of whether he has shown proof that a lipid assembly as taught by Wei would have been stable for at least six months, that an old composition does not become patentable upon the discovery of a new property. The examiner states that the liposomal preparations on column 15, Table 1, first and third lines, of Wei appear to read on all of the structural elements of the present claims. With respect to applicant's assertion of unexpected results, the examiner states that applicant has not pointed to a specific location in the specification or provided additional evidence to show these unexpected results. This rejection is respectfully traversed.

Certain errors have been noted in the examiner's arguments and these must be corrected. The examiner states in the last paragraph of page 3 that the liposomal preparations shown at column 15, Table 1, first and third line, of Wei consist of phosphatidylcholine, cholesterol,

and C2 or C6 ceramide, "which appear to read on all of the structural elements of the instant claims." This is simply a misstatement of fact. The composition of claim 1 requires a biologically active non-liposome forming lipid. The ceramide of Wei meets this requirement. It also requires a liposome forming lipid. The phosphatidylcholine of Wei meets this requirement. However, claim 1 also requires a lipopolymer having a hydrophobic lipid region and a hydrophilic polymer headgroup wherein the atomic mass ratio between the headgroup and hydrophobic region is at least 1.5. Cholesterol is not such a lipopolymer. There is nothing in Table 15 which meets the requirement of paragraph 1(b).

In the previous Official Action, the examiner noted that Wei discloses polyethylene glycol in the sentence bridging columns 13 and 14. It is the addition of this compound which is exactly the picking and choosing from the disclosures of Wei to which the examiner has previously referred. There is not a single example in Wei of a composition that includes all of the ingredients of the present claims. One would have to select polyethylene glycol from the list of optional ingredients in the lengthy disclosure of Wei, and insert it into the compositions of Table 1 of Wei in order to arrive at a composition that is

arguably within the scope of the present claims. Thus, the examiner is incorrect in stating that applicant is merely arguing an inherent property of a known composition. Applicant's composition is not known, it is novel. The properties of applicant's novel composition may be inherent but they were not known in the prior art. As stated in *In re Dillon*, 919 F.2d 688, 718 (Fed. Cir. 1990):

> Inherency and obviousness are distinct concepts. *In re Spormann*, 53, C.C.P.A. 1375, 363 F.2d 444, 448, 150, USPQ 449, 452 (CCPA 1966):
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> > The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.

Certainly it was not known at the time of the present invention that the liposomes presently claimed could achieve a stability of over six months.

As to evidence of unexpected results, the examiner's attention is invited to Table 4 at pages 56 to 58 of the present specification. This shows the physical stability properties of a number of comparative liposome compositions. First, reference is made to comparative examples 18 and 21. These include phosphatidylcholine and ceramide but no lipopolymer, such as PEG. These examples are very close to the compositions of the examples of Wei.

Both of these show that the physical stability lasts significantly less than the six months required by the present claims. One of ordinary skill in the art reading the present specification would not expect that any of the compositions of Wei would have a physical stability any longer than those of these comparative examples. It should be noted that Wei does not have any specific disclosure of physical stability parameters.

Furthermore, all of the compositions of Wei contain significant amounts of cholesterol. However, example 26 of Table 4 of the present specification shows that when cholesterol is present (in an amount of 37%), the stability drops to only one week. Furthermore the present specification states at page 71, second full paragraph:

> In addition, it was found that when cholesterol is included in the liposome to form a formulation of EPC/chol/^{2k}PEG-DSPE/C6 Cer (44/37/7.5/23) the resulting liposomes were physically unstable and decomposed within a week (No. 26 in Table 4 above).

While this does not mean that there can be no cholesterol in the formulation, it is clear that it has a destabilizing effect and when used in the large amounts as used in the compositions of Wei, one would expect a significant loss of stability, i.e., that none of the compositions of Wei would have a physical stability of six months. Small amounts of cholesterol that do not affect the six month stability of

the composition as whole, are not excluded by the present claims. However, claim 1 does specify that the components must be selected so as to obtain the specified stability.

Table 4 of the present specification shows that most of the compositions within the scope of claim 1 have a stability of greater than six months. While some have a shorter period of physical stability, these would be considered exceptions to the rule and, in any event, do not fall within the scope of present claim 1 in view of the requirement that the components be selected so as to provide the required stability..

It should be noted that the term "stable lipid assembly" is fully defined at page 9 of the present specification. Furthermore, the tests used to determine chemical and physical stability are defined in the present specification in the section bridging pages 42 and 43. Accordingly, while specific analytical parameters were requested by the examiners in the course of the interview, it is urged that this should not be necessary as the analytic tests conducted to determine the physical stability are disclosed in specification and the presumptively accurate results disclosed in the specification should be accepted without having to be backed up by a declaration of the inventors.

Accordingly, reconsideration and withdrawal of this rejection are requested in view of following factors:

- The present claims require that the components of the lipid assembly be selected such that the lipid assembly is chemically and physically stable under storage conditions of 4°C in biological fluids, for at least six months;
- None of the compositions exemplified in Wei include all three of the ingredients required in claim 1 of the present application;
- Particularly in view of Examples 18, 21 and 26 in Table 4 of the present specification, those of ordinary skill in the art reading the present specification would not expect that any of the exemplified liposomes of Wei (the closest prior art) would have the properties required by claim 1, i.e., physical stability for at least six months.

Accordingly, all of the compositions within the scope of the present claims have properties that are unexpectedly superior to the properties of the closest compositions of the prior art. It would not have been expected by one of ordinary skill in the art at the time of the present invention that by selecting PEG as an ingredient of the

liposomes of Wei, one could select compositions having the unexpected property of stability for at least six months. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 6-8 have been rejected under 35 USC 103, as being unpatentable over Wei, as applied to claim 5 above, and further in view of Cuvillier. This rejection is respectfully traversed.

Cuvillier adds nothing to the deficiencies of Wei discussed above, nor does it create any expectation that adding polyethylene glycol will permit one to select a composition having stability for at least six months. Accordingly, this rejection must fall for the same reason as discussed above with respect to the rejection of the independent claims. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 3, 11 and 13 have been rejected under 35 USC 103(a) as being unpatentable over Wei as applied to claim 1 above and further in view of Nicholas as evidenced by Tirosh. This rejection is respectfully traversed.

Nicholas and Tirosh add nothing to the deficiencies of Wei discussed above, nor do they create any expectation that adding polyethylene glycol will permit one to select a composition having stability for at least six

months. Accordingly, this rejection must fall for the same reason as discussed above with respect to the rejection of the independent claims. Reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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